

PATENT COOPERATION TREATY

1 FD

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

WOLF, GREENFIELD & SACKS, P.C.
Attn. Oyer, Timothy J.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210-2206
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

<p>Date of mailing (day/month/year) 03/04/2009</p>	
<p>Applicant's or agent's file reference C1256.70000</p>	<p>FOR FURTHER ACTION See paragraphs 1 and 4 below</p>
<p>International application No. PCT/US2008/005577</p>	<p>International filing date (day/month/year) 01/05/2008</p>
<p>Applicant CLAROS DIAGNOSTICS, INC.</p>	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

RECEIVED

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Wolf, Greenfield & Sacks, P.C.
José-Antonio Almalé Murillo
APR 20 2009

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1 *bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43 *bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference C1256.70000	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2008/005577	International filing date (day/month/year) 01/05/2008	(Earliest) Priority Date (day/month/year) 04/05/2007
Applicant CLAROS DIAGNOSTICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6b/s(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1A
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☒ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/005577

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01L3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 184 029 B1 (WILDING PETER [US] ET AL) 6 February 2001 (2001-02-06)	1,2, 10-20, 30, 37-40, 47-51
Y	column 3, line 34 - line 43; figures 4,6A,7,9,10A column 9, line 56 - column 12, line 9	3-9,22, 31-33
X	US 5 731 212 A (GAVIN MICHAEL [US] ET AL) 24 March 1998 (1998-03-24)	1-4, 7-11,19, 20, 30-40, 47-51
Y	figures 6,7A-7D	5,6, 12-18,22

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search

26 March 2009

Date of mailing of the international search report

03/04/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

de Biasio, Arnaldo

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/005577

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/115094 A1 (GUMBRECHT WALTER [DE] ET AL) 17 June 2004 (2004-06-17) claims 1,8-13,17,19; figures 1-4 -----	1
Y	US 2006/094119 A1 (ISMAGILOV RUSTEM F [US] ET AL) 4 May 2006 (2006-05-04) claims 1,20-22; figures 5,6 -----	3-9, 31-33
Y	US 2003/082081 A1 (FOUILLET YVES [FR] ET AL) 1 May 2003 (2003-05-01) claim 1 -----	3-9, 31-33
Y	WO 2006/113727 A (HARVARD COLLEGE [US]; LINDER VINCENT [CH]; SIA SAMUEL K [US]; WHITESID) 26 October 2006 (2006-10-26) cited in the application page 10, line 6 - line 31; claims 1,7; figures 1A,1B,2B,9 -----	12-18, 22,31-33
X	WO 2005/056186 A (TRINITY COLLEGE DUBLIN [IE]; VIVIANNE WILLIAMS [IE]; IGOR SCHVETS [IE]) 23 June 2005 (2005-06-23) page 9, line 25 - page 10, line 32; figures 1-9,12 -----	52-55
X	WO 2006/018044 A (AGILENT TECHNOLOGIES INC [US]; BERNDT MANFRED [DE]; GASSMANN MARCUS [D]) 23 February 2006 (2006-02-23) paragraph [0059]; figures 1-5 -----	56-61
X	US 2005/161669 A1 (JOVANOVICH STEVAN B [US] ET AL) 28 July 2005 (2005-07-28) paragraphs [0199] - [0207]; figures 1-4,7,9,11-13,16,20 -----	56-61
X	US 2004/228771 A1 (ZHOU PENG [US] ET AL) 18 November 2004 (2004-11-18) figures 1-12 -----	52-55

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/005577

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-20, 22, 47-61
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20,22,47-51

microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path containing a reagent, the microfluidic device being constructed so as to operate without ricirculation

2. claims: 21,41,42

microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path comprising a volume control element

3. claims: 23-24,27-29

microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path, the fluidic connector comprising a non-fluidic feature so as to form a non-fluidic connection between the fluidic connector and the substrate

4. claims: 25,26,43-46

microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path, the fluidic connector comprising a sampling element

5. claims: 30-40

microfluidic device having a substrate with a two separate microfluidic channels, each channel containing a reagent, wherein the channels are not in fluid communication with one another prior to a first use but are brought into fluid communication at first use; claims 34-40 define related methods

6. claims: 52-61

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path, the microfluidic device further comprising an alignment element

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/005577

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6184029	B1	06-02-2001	NONE	
US 5731212	A	24-03-1998	NONE	
US 2004115094	A1	17-06-2004	AT 327830 T	15-06-2006
			CA 2439924 A1	19-09-2002
			WO 02072262 A1	19-09-2002
			DE 10111457 A1	19-09-2002
			DK 1381466 T3	02-10-2006
			EP 1381466 A1	21-01-2004
			JP 2004532395 T	21-10-2004
US 2006094119	A1	04-05-2006	NONE	
US 2003082081	A1	01-05-2003	NONE	
WO 2006113727	A	26-10-2006	AU 2006236410 A1	26-10-2006
			CA 2604323 A1	26-10-2006
			EP 1872111 A2	02-01-2008
			JP 2008537146 T	11-09-2008
WO 2005056186	A	23-06-2005	AU 2003292497 A1	29-06-2005
			US 2008107565 A1	08-05-2008
WO 2006018044	A	23-02-2006	US 2007154355 A1	05-07-2007
US 2005161669	A1	28-07-2005	NONE	
US 2004228771	A1	18-11-2004	WO 2004103562 A2	02-12-2004

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2008/005577

International filing date (day/month/year)
01.05.2008

Priority date (day/month/year)
04.05.2007

International Patent Classification (IPC) or both national classification and IPC
INV. B01L3/00

Applicant
CLAROS DIAGNOSTICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

de Biasio, Arnaldo

Telephone No. +49 89 2399-8627



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2008/005577

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2008/005577

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 21, 23-46

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for the whole application or for said claims Nos. 21, 23-46

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2008/005577

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-20,22,30-40,47-61

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>3-9,11,14-20,22,47-51,53,57,59,60</u>
	No: Claims	<u>1,2,10,12,13,52,54,55,56,58, 61</u>
Inventive step (IS)	Yes: Claims	=
	No: Claims	<u>1-20,22,47-61</u>
Industrial applicability (IA)	Yes: Claims	<u>1-20,22,47-61</u>
	No: Claims	=

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2008/005577

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

This Authority considers that there are six Inventions covered by the claims indicated as follows:

- Group I: microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path containing a reagent, the microfluidic device being constructed so as to operate without ricirculation (claims 1-20,22, 47-51).
- Group II: microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path comprising a volume control element (claims 21,41,42).
- Group III: microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path, the fluidic connector comprising a non-fluidic feature so as to form a non-fluidic connection between the fluidic connector and the substrate (claims 23-24,27-29).
- Group IV: microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path, the fluidic connector comprising a sampling element (claims 25,26,43-46).
- Group V: microfluidic device having a substrate with a two separate microfluidic channels, each channel containing a reagent, wherein the channels are not in fluid communication with one another prior to a first use but are brought into fluid communication at first use (claims 30-33, claims 34-40 define related methods).
- Group VI: microfluidic device having a substrate with a two separate microfluidic channels and a fluidic connector for fluidically connecting said two microfluidic channels by means of a fluid path, the microfluidic device further comprising an alignment element (claims 52-61).

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The subject-matter of claim 1 is not novel (Art. 33(2) PCT) over US-B-6,184,029 (D1).

D1 discloses a device (cf figures 4, 6A and 7 of D1) comprising:

- a microfluidic system (cf appliance 30, 50 and 90 in D1) formed in a substrate comprising a first microfluidic channel including at least one inlet and one outlet and a second microfluidic channel including at least one inlet and one outlet; and
- a fluidic connector (cf "sample preparation device" 10) that can be connected to the substrate comprising a fluid path including a fluid path inlet and a fluid path outlet, wherein upon connection, the fluid path inlet connects to the outlet of the first micro fluidic channel to allow fluid communication between the fluid path and the first microfluidic channel, and the fluid path outlet connects to the inlet of the second microfluidic channel to allow fluid communication between the fluid path and the second microfluidic channel,
- wherein the fluid path contains a reagent (cf col. 10, ll. 44-67) disposed therein prior to connection of the fluidic connector to the substrate, and
- wherein the microfluidic system is suitable for operating without recirculation of a fluid in the system.

The subject-matter of claim 1 is also known from US-A-2004/0115094 (cf figures 1,2).

As the subject-matter of claim 1, i.e. of the independent claim of group I, is not novel and not inventive (Art. 33(3) PCT), it cannot share a common inventive concept with the subject-matter of the other groups of potential inventions (Rule 13.1 PCT).

From the discussion of D1, it also clearly appears that the common part (microfluidic substrate and fluid connector) shared by groups I-IV and VI is known from prior art. Moreover, said groups of inventions address different problems with different special technical features (Rule 13(2) PCT):

The subject-matter of group I addresses the problem of storing a reagent. Its special technical features are a reagent disposed in the fluid path in the fluid connector and the construction of the system not allowing recirculation of a fluid.

The subject-matter of group II addresses the problem of introducing a controlled volume of fluid into the fluid path prior to connection of the fluidic connector with the microfluidic system. The corresponding special technical feature is a volume control element as defined in claims 21 and 41.

The subject-matter of group III addresses the problem of forming a non-fluidic connection between the fluidic connector and the substrate with the special technical features as functionally defined in claims 23 and 27.

The subject-matter of group IV addresses the problem of providing device with means for taking a sample of a biological entity as defined in claims 25 and 43.

The subject-matter of group VI addresses the problem of aligning the fluidic connector and the microfluidic substrate. this is achieved with the special technical features of claims 52, 56 and 61.

Hence, the subject-matter of the groups I-IV and VI address different technical problems with different special technical features and there is no technical relationship among these potential inventions (Rule 13.2 PCT).

The subject-matter of group VI, as that of group I, addresses a problem of storing reagents. In this case storage is performed in the microfluidic substrate, not in the fluidic connector. As already mentioned above, the subject-matter of claim 1 being not novel it cannot form a common inventive concept with that of group VI. Nor can the subject-matter of group VI share a common inventive concept with anyone of groups II-IV or VI, as it addresses a different problem with different special technical features.

Only the subject-matter of groups I and VI have been searched. Consequently, only this subject-matter can be examined in what follows.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1.1 As already discussed under item IV, the subject-matter of claim 1 is not novel (Art. 33(2) PCT) over US-B-6,184,029 (D1).

Also US-A-2004/0115094 (D2) should be novelty destroying for the subject-matter

of present claim 1 (see D2, figures 1-4).

Moreover, the subject-matter of claim 1 should be obvious in view of US-A-5,731,212 (D3), of embodiments of figures 6, 7A-7D. Valve manifold 112 being the fluid connector and e.g. channels 124 and 123 being first and second channel in the substrate. The only feature of claim 1 which is not explicitly mentioned in D3 is the one specifying that the substrate is of microfluidic size. However, to miniaturize the device of D3 is straightforward for the skilled person (Art. 33(3) PCT).

1.2 Dependent claims 2-20,22 and 47-51 do appear to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, reference is made to the passages cited in the search report.

2.1 The device of claim 52 is not novel (Art. 33(2) PCT) over WO-2005/056186 (D4).

D4 discloses (see figures 1-7, 12) a device comprising:

- a substrate (12) comprising a microfluidic system (cf input module 15 and microchannel module 17) including a first microfluidic channel (see channels of input module 15) including an inlet and an outlet and a second microfluidic channel (see channels 37 in microfluidic module 17) including an inlet and an outlet;
- a fluidic connector (18, see figure 3) constructed for matching connection to the substrate (see figure 2 and steps 1-10 on pages 9-10), comprising a fluid path including a fluid path inlet and a fluid path outlet, wherein upon connection of the fluidic connector to the substrate, the fluid path inlet is suitable for connecting to the outlet of the first microfluidic channel (in the input module) and the fluid path outlet is suitable for connecting to the inlet of the second microfluidic channel; and
- an alignment element (30, see figure 7) associated with the substrate, extending from the substrate and comprising a cavity (31) constructed and arranged to receive and engage the fluidic connector (see figures 2 and 8) and thereby position the connector in a predetermined, set configuration relative to the substrate,
- wherein the fluidic connector is adapted to be inserted into the alignment

element by sliding motion.

Although D4 does not disclose the fluid connector in a configuration wherein it is connecting a channel of the input module with a channel of the microfluidic module, said fluid connector is suitable for such a connection. Hence, D4 discloses all the features of present claim 1 (Art. 33(2) PCT).

2.2 Also US-A-2004/0228771 (D5) should be novelty destroying for the device of claim 1 (Art. 33(2) PCT).

The substrate is represented by plate 70 ("alignment base") and fluidic chips 10 positioned in the lower cavities of plate 70. The connector is represented by fluidic chips 10 in the upper cavities (cf figure 11). As can be seen in figures 7 and 8, the alignment elements for the upper fluidic chips comprise a cavity suitable for positioning the fluidic connectors (i.e. the fluidic chips 10) in a predetermined configuration. Also the insertion of fluidic chips 10 in plate 70 is obtained by a sliding motion.

2.3 The subject-matter of claim 56 is not novel (Art. 33(2) PCT) over WO-2006/018044 (D6):

D6 discloses (see figures 1 and 3) a device (microfluidic assembly 1) comprising:

- a substrate comprising a microfluidic system (microfluidic devices 7 and 9) including a first microfluidic channel (17) including an inlet and an outlet and a second microfluidic channel (17) including an inlet and an outlet;
- a fluidic connector (slider 21) constructed for matching connection to the substrate (see figure 1), comprising a fluid path including a fluid path inlet and a fluid path outlet, wherein upon connection of the fluidic connector to the substrate, the fluid path inlet is suitable for connecting to the outlet of the first microfluidic channel and the fluid path outlet is suitable for connecting to the inlet of the second microfluidic channel; and
- an alignment element (interface 5) associated with the substrate constructed and arranged to receive and engage the fluidic connector and thereby position the connector in a predetermined, set configuration relative to the substrate-
- wherein the alignment element comprises an engaging component

(actuators 93) constructed and arranged to engage a portion of the fluid connector to create a substantial resistance to movement of the fluidic connector relative to the alignment element upon the alignment receiving component (see par. [0059]).

Hence, the device of claim 56 is not novel over D6 (Art. 33(2) PCT).

A similar objection under Art. 33(2) PCT can be raised in view of US-A-2005/0161669 (D7), reference is made to the passages cited in the search report.

- 2.4 Dependent claims 53-55 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, reference is made to the passages cited in the search report.

Re Item VII

Certain defects in the international application

1. The independent claims have not been drafted in the two-part form (Rule 6.3(b) PCT).
2. The features in the claims have not been provided with reference signs (Rule 6.2(b)).

Re Item VIII

Certain observations on the international application

1. According to the description (cf page 2, ll. 8-10) one major problem addressed by the present application should be the reduction of dead volumes. It is not clear, however, by means of what features in the claims this problem is addressed (Art. 6 PCT).

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information

For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.

Amending claims under Art. 19 PCT

Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.

Filing a demand for international preliminary examination

In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT).

If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).

Filing informal comments

After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.

End of the international phase

At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).

Relevant PCT Rules and more information

Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003